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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional): 6460-18-1

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Signature _____

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Application Number	Filed
09/868,469	September 24, 2001

First Named Inventor: BENKOVIC S.J.

Art Unit	Examiner
1652	Fronda, C. J.

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

- [ ] applicant/inventor.
- [ ] assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)
- [X] attorney or agent of record. Registration number 56,712.
- [ ] attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34 _____

Signature

Nicholas A. Zachariades, Ph.D.
Typed or printed name

561-653-5000
Telephone number

January 23, 2007
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

[X] *Total of 1 forms are submitted.

This collection of information is required by 35 U.S.C. 132. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11, 1.14 and 41.6. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Application of:	Benkovic S. J., et al.	Confirmation No:	1582
Application No.:	09/868,469	Examiner:	Fronda C. L.
Date Filed:	September 24, 2001	Group:	1652

For: CYCLIC PEPTIDES

Attn: **Mail Stop AF**
Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Dear Sir:

In response to the final Office Action dated October 23, 2006, Applicant respectfully files herewith a Notice of Appeal and requests review of the present application before filing an appeal brief.

Related Appeals

The issues presented in the present application are not related to any pending appeal.

Status of the Claims

Claims 1-127 are pending in the application. Claims 1-11, 14-40 and 53-89 have been rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement.

Clear Errors for Review

Applicants respectfully assert that the specification provides a sufficient description to allow one of ordinary skill in the art to "make and use" the instant invention. The instant invention is directed in part to a nucleic acid molecule encoding a polypeptide comprising a first carboxy-terminal portion of a split intein (C-intein), a second amino-terminal portion of a split intein (N-intein), and a target peptide flanked on one end with the carboxy-terminal portion of a split intein (C-intein) and on its other end with the amino-terminal portion of a split intein (N-intein); wherein expression of the nucleic acid molecule in a host system produces the polypeptide in a form selected from the group consisting of: (a) a polypeptide that spontaneously splices in the host system to yield a cyclized form of the target peptide, and (b) a splicing

intermediate of a cyclized form of the target peptide. Applicants describe on page 5, lines 3-12, the method for producing and screening of cyclic peptide libraries *in vivo*:

> A general method for the *in vivo* production and screening of cyclic peptide libraries has been discovered. In this method, a nucleic acid molecule is constructed such that a nucleotide sequence encoding the peptide to be cyclized is flanked on one end with a nucleotide sequence encoding the **carboxy-terminal portion** of a split (or trans) intein (C-intein or I_C) and on its other end with a nucleotide sequence encoding the **amino-terminal portion** of a split intein (N-intein or I_N). Expression of the construct within a host system such as a bacterium or eukaryotic cell results in the production of a fusion protein. The two split intein components (i.e., I_C and I_N) of the fusion protein then assemble to form an active enzyme that splices the amino and carboxy termini together to generate a backbone cyclic peptide. (Emphasis added).

The Examiner asserts that the claims are "genus claims that are directed toward a genus of inteins; a genus of split inteins; a genus of split inteins ....The scope of each genus includes many members with widely differing structural, chemical, and physiochemical properties. Furthermore, each genus is highly variable because a significant number of structural differences between genus members exists."

Applicants respectfully disagree with the Examiner's assertions that "the disclosure of these polynucleotides is insufficient to be representative of the attributes and features of all species encompassed by the claims." Applicants submit that the sequences of these inteins are known and the common structural feature which is inherent of each intein, irrespective of the genus, is the **ability to be cleaved and reassemble**. Furthermore, MPEP § 2163, states that "the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying

characteristics, sufficient to show the applicant was in possession of the claimed genus. See *Eli Lilly,* 119 F.3d at 1568, 43 USPQ2d at 1406." (Emphasis added).

Applicants provide sufficient written description as to selection of inteins. For example, a first portion and a second portion is an N-terminal portion of a split intein and a carboxy-terminal portion of a split intein wherein each portion alone has no activity and requires the assembly of these portions to form an active enzyme. The number of amino acids that comprise each portion is not important, but the fact that assembly of each portion must form an **active** enzyme. Applicants further teach examples of split inteins. See, for example, page 6, lines 16-19:

> Both the **first portion** of a split intein and the **second portion** of a split intein can be derived from a naturally-occurring split intein such as Ssp DnaE. In other variations, one or both of split intein portions can be derived from non-naturally occurring split inteins such as those derived from RecA, DnaB, Psp Pol-I, and Pfu inteins. (Emphasis added).

Applicants teach that the N- and C-terminal **inteins are proteins that actually associate** to form a complex that initiates and drives the cyclization reaction. (See for example, page 18, lines 5-23 through to page 2, lines 1-12 and figures 1 and 2). Within this complex the cyclization reaction occurs with the concomitant loss of the N- and C-terminal inteins. Applicants also teach that the portions of split inteins can be naturally occurring or artificially produced. See, for example, page 20, lines 11-24 through to page 21, lines 1-13:

> Nucleotide sequences that encode the first portion of a split intein and the second portion of a split intein of the nucleic acid molecules within the invention can be derived from **known inteins.** A fairly comprehensive and descriptive list of such inteins is published by New England Biolabs at http//www.neb.conljinteins/ifltreghtml **Any of these known inteins can be used as long as they are compatible with invention**.
>
> Nucleotide sequences that encode either naturally-occurring or artificially-produced split inteins can be used to generate the intein portions of nucleic acid molecules within the invention. Naturally-occurring split inteins are expressed in nature as two separate components that bind one another to form one active splicing agent. The nucleic acid molecules encoding these naturally-occurring components can thus be used in the invention. One example of a naturally-occurring split intein

> that may be used is Ssp DnaE (Wu et al, Proc. Natl. Acad. Sci. USA 95:9226,1998).
>
> Inteins that are not split in their natural state (i.e., those that exist as one continuous chain of amino acids) can be artificially split using known techniques. For example, two or more nucleic acid molecules encoding different portions of such inteins can be made so that their expression yields two or more artificially split intein components. See, e.g., Evans *et al, J. Biol. Chem.* 274:18359, 1999; Mills *et al, Proc. Natl. Acad. Sci.* USA 95:3543, 1998. The nucleic acids that encode such non-naturally occurring intein **components (portions)** can be used in the invention. Those nucleic acid molecules that encode non-naturally occurring split intein portions which efficiently interact on the same precursor polypeptide to yield cyclic peptides or splicing intermediates are preferred. Examples of non-naturally occurring split inteins from which such nucleic acid molecules can be derived include Psp Pol- 1 (Southworth, M.W., et al, *The EMBO J.* 17:918, 1998), Mycobacterium tuberculosis RecA intein, (Lew, B.M., *et al, J. Biol. Chem.* 273:15887, 1998; Shingledecker, K., *et al, Gene* 207:187, 1998; Mills, K.V., *et al, Proc. Natl. Acad. Sci.* USA 95:3543, 1998), Ssp DnaB/Mxe GyrA (Evans, T.C. *et al, J. Biol. Chem.* 274:18359, 1999), and Pfu (Otomo *et al, Biochemistry* 38:16040, 1999; Yamazaki *et al, J. Am. Chem. Soc.* 120:5591, 1998). (Emphasis added).

Applicants submit, that inteins can be used based on the instant teachings. Examples are taught within the specification and in the originally filed claims. Applicants provide more than is necessary to fulfill the written description requirement.

MPEP § 2163 also states in pertinent part:

> An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.,* 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Elecs., Inc.,*

> 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406; *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it"). "Compliance with the written description requirement is essentially a fact-based inquiry that will 'necessarily vary depending on the nature of the invention claimed.'" *Enzo Biochem*, 323 F.3d at 963 , 63 USPQ2d at 1613.

Applicants further describe, in detail, the invention and that inteins (RecA, DnaB, Psp, Pol-I or Pfu inteins) as claimed, are suitable in the methods of the invention. These inteins can be used to produce multiple split inteins. Indeed, knowledge of inteins in the art, is such that the mere recitation of the word "intein" immediately conjures **a genus of functionally equivalent protein sequences** in the mind of the person of skill in the art which, when provided with the teachings of the present disclosure, readily allows the artisan to make and use the claimed invention. According to MPEP 2163, "[i]f a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met."

Accordingly, it is respectfully submitted that the claims are in condition for allowance and clear error has been committed in the final Office Action. The Commissioner is hereby authorized to charge any additional fees which may be required at any time during the prosecution of this application without specific authorization, or credit any overpayment, to Deposit Account Number 50-0951.

Respectfully submitted,
AKERMAN SENTERFITT

Date: January 23, 2007

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Docket No. 6818-18-1